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(54) Title: USE OF LOW MOLECULAR WEIGHT THROMBIN INHIBITORS IN CHOLESTEROL-LOWERING THERAPY

(57) Abstract: According to the invention there is provided the use of a low molecular weight thrombin inhibitor, or a pharmaceuti-
cally acceptable derivative thereof, for the manufacture of a medicament for use in cholesterol-lowering therapy and/or modification
of lipid (triglyceride), lipoprotein, and apolipoprotein, profiles associated with an increased risk of cardiovascular complications.

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**USE OF LOW MOLECULAR WEIGHT THROMBIN INHIBITORS
IN CHOLESTEROL-LOWERING THERAPY**

Field of the Invention

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This invention relates to a new use of low molecular weight thrombin inhibitors.

Background and Prior Art

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It is well known that high levels of cholesterol are associated with heart disease. More than half of all US citizens are understood to have cholesterol levels that exceed those recommended, and one in five has cholesterol levels that are considered high.

15

Cholesterol is involved in the production and maintenance of cell membranes, as well as the production of sex hormones (including progesterone, testosterone, estradiol and cortisol), bile salts and Vitamin D. It is formed primarily in the liver, but also in other parts of the body, such as
20 the small intestine.

25

In healthy individuals, all of the cholesterol that is needed to perform the above-mentioned functions is produced naturally. However, in a typical blood test, of the amount of cholesterol circulating in blood, about 85% is endogenous, the other 15% arising from external sources. Dietary cholesterol usually originates from meat, poultry, fish, seafood and dairy products. In this respect, high consumption levels of these foodstuffs may give rise to increased cholesterol levels in the bloodstream.

Increased cholesterol levels in serum have been associated with atherosclerosis, which is known to increase significantly the risk of blood vessel blockage (stenosis), and thus the likelihood of angina pectoris, myocardial infarction and other cardiovascular complications, such as stroke.

Cholesterol is insoluble in aqueous environments and thus needs to be transported within the bloodstream by apolipoproteins (Apos). When apolipoproteins are associated with cholesterol, complexes known as lipoproteins are formed. The density of these lipoproteins is determined by the amount of protein in the molecule and, in this respect, low-density lipoproteins (LDLs), which are the major cholesterol carrier in the blood, are known to have more of the negative effects mentioned herein than protective high-density lipoproteins (HDLs). High levels of LDLs are thus associated with atherosclerosis, whereas greater levels of HDLs are understood to provide some protection against stenosis, and hence coronary risk, by way of removal of excess cholesterol (transporting it to the liver for disposal).

A third group of carrier molecules, very low-density lipoproteins (VLDLs) are converted to LDLs following the delivery of triglycerides to the muscles and adipose tissue. Triglycerides are a mixture of fatty acids and glycerol and are the major components of lipids circulating in blood. Like cholesterol, triglycerides are substances that are found endogenously in the bloodstream, and may be deposited in adipose tissue. Triglycerides contain high-energy fatty acids which provide much of the fuel needed for normal cellular function. However, an excessive amount of triglycerides, or VLDLs, in the bloodstream can result in similar problems to those

associated with high cholesterol and LDL levels, as well as obesity and diabetes.

Thus, levels of HDLs, LDLs, total cholesterol and triglycerides are all key
5 indicators in determining the risk of atherosclerosis and associated
cardiovascular disorders, such as coronary artery diseases (e.g. angina
pectoris, myocardial infarction, etc.), stroke (including cerebro-vascular
accident and transient ischaemic attack), peripheral arterial occlusive
disease, obesity and diabetes. Patients with high overall cholesterol and/or
10 triglycerides levels are at a significant risk, irrespective of whether or not
they also have a favourable HDL level. Patients with normal cholesterol
levels but low HDL levels are also at increased risk. Recently, it has also
been noted that the level of risk of cardiovascular disease associated with
high levels of apolipoprotein B (ApoB; which carries lipids in VLDLs and
15 LDLs), and/or low levels of apolipoprotein A-I (ApoA-I; which carries
lipids in HDLs), is extremely high.

There are numerous factors that influence cholesterol and triglyceride levels,
including diet, age, weight, gender, genetics, diseases (such as diabetes) and
20 lifestyle.

Positive changes in relation to diet, lifestyle and exercise are often
insufficient to decrease the risk of cardiovascular problems. In such
instances, cholesterol- and/or triglyceride-lowering medication may be
25 prescribed.

Drugs that reduce LDL levels in serum can prevent or reduce the build-up of
artery blocking plaques, and can reduce the risk of plaque rupture and
associated thrombo-embolic complications. There are several types of drugs

that can help reduce blood cholesterol levels. The most commonly prescribed are the statins, HMG-CoA reductase inhibitors, such as lovastatin, pravastatin, fluvastatin, simvastatin, atorvastatin, pitavastatin and rosuvastatin (e.g. rosuvastatin-calcium). These drugs prevent directly the formation of cholesterol in the liver and thus reduce the risk of cardiovascular disease. Other prescribed drug categories include resins (such as cholestyramine and colestipol), which act by binding bile acids, so causing the liver to produce more of the latter, and using up cholesterol in the process. Further, the B vitamin niacin has been reported at high doses to lower triglycerides and LDL levels in addition to increasing HDL levels. Fibrates (such as gemfibrozil and fenofibrate) are known to lower triglycerides and can increase HDL levels.

However, some of these drugs are known to have side effects, including liver damage. Hence, there is a need for alternative and/or more effective drugs for use in cholesterol-lowering therapy.

The early development of low molecular weight inhibitors of thrombin has been described by Claesson in Blood Coagul. Fibrinol. (1994) 5, 411. Low molecular weight thrombin inhibitors (and prodrugs thereof) have been described more recently in US Patent N° 4,346,078; International Patent Applications WO 93/11152, WO 93/18060, WO 93/05069, WO 94/20467, WO 94/29336, WO 95/35309, WO 95/23609, WO 96/03374, WO 96/06832, WO 96/06849, WO 96/17860, WO 96/24609, WO 96/25426, WO 96/32110, WO 97/01338, WO 97/02284, WO 97/15190, WO 97/23499, WO 97/30708, WO 97/40024, WO 97/46577, WO 98/06740, WO 97/49404, WO 97/11693, WO 97/24135, WO 97/47299, WO 98/01422, WO 98/57932, WO 99/29664, WO 98/06741, WO 99/37668, WO 99/37611, WO 98/37075, WO 99/00371, WO 99/28297, WO 99/29670, WO 99/40072, WO 99/54313, WO 96/31504,

WO 00/01704, WO 00/08014, WO 00/35859, WO 00/35869, WO 00/42059,
WO 00/61577, WO 00/61608, WO 00/61609, WO 01/87879, WO 02/14270,
WO 02/44145, WO 03/000653, WO 04/000818 and WO 04/014894; and
European Patent Applications 648 780, 468 231, 559 046, 641 779, 185 390,
5 526 877, 542 525, 195 212, 362 002, 364 344, 530 167, 293 881, 686 642,
669 317, 601 459 and 623 596.

In particular, international patent application WO 94/29336 discloses a
group of compounds, including $\text{HOOC-CH}_2\text{-(R)Cgl-(S)Aze-Pab-H}$ (in which
10 Cgl represents cyclohexylglycyl, Aze represents azetidine-2-carboxyl and
Pab-H represents 4-amidinobenzylamino), which is also known as
melagatran (see Example 1 of WO 94/29336). International Patent
Application WO 97/23499 discloses prodrugs of *inter alia* melagatran.

15 More recently, international patent application WO 02/44145 discloses α -
hydroxy acid-based low molecular weight thrombin inhibitors and prodrugs
thereof.

To the applicant's knowledge, none of the above-mentioned documents
20 disclose or suggest the direct use a low molecular weight thrombin inhibitor
or a prodrug thereof in cholesterol-lowering therapy and/or modifications of
lipid (including triglyceride), lipoprotein, or apolipoprotein, profiles.

Disclosure of the Invention

25

We have found, surprisingly, that administration of a low molecular weight
thrombin inhibitor may give rise to reduced levels of lipids, such as total
cholesterol, LDLs (i.e. LDL-cholesterol) and triglycerides in the
bloodstream, in addition to increasing HDL (i.e. HDL-cholesterol) levels.

According to a first aspect of the invention there is provided the use of a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for use in
5 cholesterol-lowering therapy.

When employed in the context of the present invention and disclosure, the term "cholesterol-lowering therapy" includes any therapy that results in beneficial modifications of serum profiles of total cholesterol, lipids
10 (including triglycerides), lipoproteins or apolipoproteins, and will thus be understood to encompass the terms "lipid-modifying therapy" and "lipid- (and triglyceride-) lowering therapy", as well as the treatment of hyperlipidaemias (i.e. the elevation of lipids in the bloodstream), including hypercholesterolaemia (high cholesterol levels in the blood; including
15 primary and secondary (combined) hypercholesterolaemia), hyperlipoproteinemia (elevated plasma lipoproteins levels) and/or hypertriglyceridemia (high triglyceride levels in the blood). The term will thus be understood to include types I, II (IIa and IIb), III, IV and/or V hyperlipoproteinaemia, as well as secondary hypertriglyceridaemia and/or
20 familial lecithin cholesterol acyltransferase deficiency, but in principle includes any treatment of a patient which results in a decrease in serum levels of cholesterol, LDLs, VLDLs, triglycerides and/or ApoB, and/or an increase in serum levels of HDLs and/or ApoA-I.

25 According to a second aspect of the invention there is provided a cholesterol-lowering therapy method, which method comprises the administration of a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative thereof, to a patient in need of such therapy.

For the avoidance of doubt, in the context of this disclosure, the terms "treatment", "therapy" and "therapy method" include the therapeutic and/or prophylactic treatment of patients in need of modifications of cholesterol, lipid (including triglyceride), lipoprotein and/or apolipoprotein profiles.

"Pharmaceutically acceptable derivatives" of thrombin inhibitors includes salts (e.g. pharmaceutically-acceptable non-toxic organic or inorganic acid addition salts) and solvates. It will be appreciated that the term further includes derivatives that have, or provide for, the same biological function and/or activity as any relevant inhibitor. Thus, for the purposes of this invention, the term also includes prodrugs of thrombin inhibitors.

The term "low molecular weight thrombin inhibitor" will be understood by those skilled in the art. The term may also be understood to include any composition of matter (e.g. chemical compound) which inhibits thrombin to an experimentally determinable degree in *in vivo* and/or in *in vitro* tests, and which possesses a molecular weight of below 2,000, preferably below 1,000.

Preferred low molecular weight thrombin inhibitors include low molecular weight peptide-based, amino acid-based, and/or peptide analogue-based, thrombin inhibitors.

The term "low molecular weight peptide-based, amino acid-based, and/or peptide analogue-based, thrombin inhibitors" will be well understood by one skilled in the art to include low molecular weight thrombin inhibitors with one to four peptide linkages, and includes those described in the review paper by Claesson in Blood Coagul. Fibrin. (1994) 5, 411, as well as those disclosed in

US Patent N° 4,346,078; International Patent Applications WO 93/11152, WO 93/18060, WO 93/05069, WO 94/20467, WO 94/29336, WO 95/35309, WO 95/23609, WO 96/03374, WO 96/06832, WO 96/06849, WO 96/17860, WO 96/24609, WO 96/25426, WO 96/32110, WO 97/01338, WO 97/02284, 5 WO 97/15190, WO 97/30708, WO 97/40024, WO 97/46577, WO 98/06740, WO 97/49404, WO 97/11693, WO 97/24135, WO 97/47299, WO 98/01422, WO 98/57932, WO 99/29664, WO 98/06741, WO 99/37668, WO 99/37611, WO 98/37075, WO 99/00371, WO 99/28297, WO 99/29670, WO 99/40072, WO 99/54313, WO 96/31504, WO 00/01704, WO 00/08014, WO 00/35859, 10 WO 00/35869, WO 00/42059, WO 00/61577, WO 00/61608, WO 00/61609, WO 01/87879, WO 02/14270, WO 02/44145, WO 03/000653 and WO 04/000818; and European Patent Applications 648 780, 468 231, 559 046, 641 779, 185 390, 526 877, 542 525, 195 212, 362 002, 364 344, 530 167, 293 881, 686 642, 669 317, 601 459 and 623 596, the specific and generic 15 disclosures in all of which documents are hereby incorporated by reference.

Preferred low molecular weight peptide-based thrombin inhibitors include those described generically and specifically in international patent application WO 98/37075, including the compound that is the subject of Claim 8 of that 20 application as published (1-methyl-2-[N-(4-amidinophenyl)aminomethyl]-benzimidazol-5-yl-carboxylic acid, N-(2-pyridyl)-N-(2-hydroxycarbonyl-ethyl)amide) and prodrugs thereof, such as the compound that is the subject of Claim 10 of that application as published (1-methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]aminomethyl]benzimidazol-5-yl-carboxylic 25 acid, N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)amide) and those described in international patent application WO 04/014894.

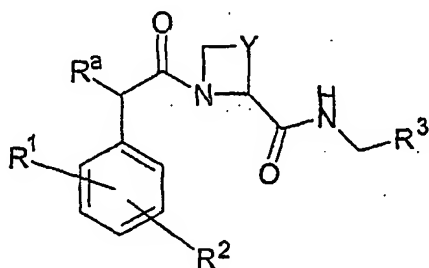
Preferred low molecular weight peptide-based thrombin inhibitors also include $\text{HOOC-CH}_2\text{-(R)Cha-Pic-Nag-H}$ (wherein Cha represents

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cyclohexylalanine, Pic represents (*S*)-pipecolinic acid and Nag represents noragmatine; known as inogatran; see International Patent Application WO 93/11152) and, especially, HOOC-CH₂-(*R*)Cgl-(*S*)Aze-Pab-H (known as melagatran; see above and International Patent Application WO 94/29336).

5

Further thrombin inhibitors include those of the formula I,



10 wherein

R^a represents -OH or -CH₂OH;

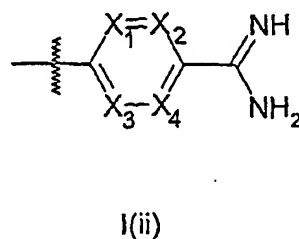
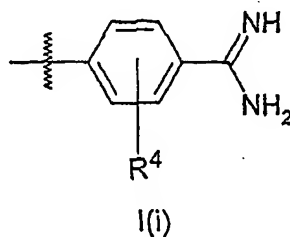
R¹ represents at least one optional halo substituent;

R² represents one or two C₁₋₃ alkoxy substituents, the alkyl parts of which substituents are themselves substituted with one or more fluoro substituents

15 (i.e. R² represents one or two fluoroalkoxy(C₁₋₃) groups);

Y represents -CH₂- or -(CH₂)₂; and

R³ represents a structural fragment of formula I(i) or I(ii):



20 wherein

R⁴ represents H or one or more fluoro substituents; and

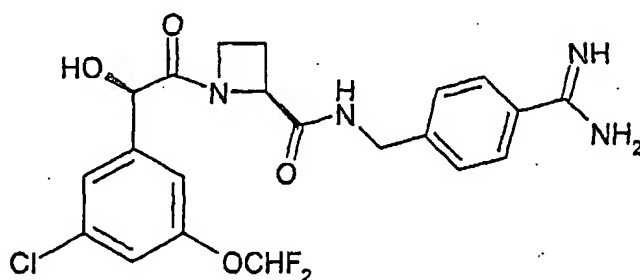
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one or two of X_1 , X_2 , X_3 and X_4 represent -N- and the others represent -CH-.

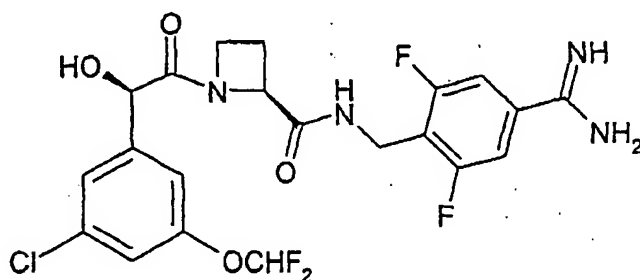
Preferred compounds of formula I include:

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(a) $\text{Ph}(3\text{-Cl})(5\text{-OCHF}_2)\text{-(R)CH(OH)C(O)-(S)Aze-Pab}$:

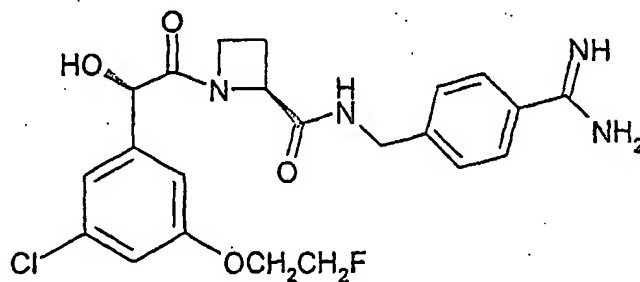


10 (b) $\text{Ph}(3\text{-Cl})(5\text{-OCHF}_2)\text{-(R)CH(OH)C(O)-(S)Aze-Pab}(2,6\text{-diF})$:



(c) $\text{Ph}(3\text{-Cl})(5\text{-OCH}_2\text{CH}_2\text{F})\text{-(R)CH(OH)C(O)-(S)Aze-Pab}$:

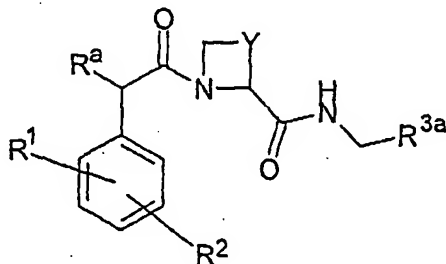
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The term "prodrug" of a low molecular weight thrombin inhibitor includes any compound that, following oral or parenteral administration, is metabolised *in vivo* to form a low molecular weight thrombin inhibitor (as defined herein), in an experimentally-detectable amount, and within a predetermined time (e.g. within a dosing interval of between 6 and 24 hours (i.e. once to four times daily)). For the avoidance of doubt, the term "parenteral" administration includes all forms of administration other than oral administration.

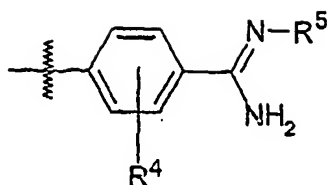
Prodrugs of the thrombin inhibitor melagatran that may be mentioned include those disclosed in international patent application WO 97/23499. Preferred prodrugs are those of the formula $R^1O_2C-CH_2-(R)Cgl-(S)Aze-Pab-OH$ (see the list of abbreviations above or in WO 97/23499), wherein R^1 represents C_{1-10} alkyl or benzyl, such as linear or branched C_{1-6} alkyl (e.g. C_{1-4} alkyl, especially methyl, propyl and, particularly, ethyl) and the OH group replaces one of the amidino hydrogens in Pab.

Preferred prodrugs of compounds of formula I that may be mentioned include those of formula Ia,

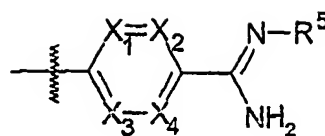


Ia

wherein R^{3a} represents a structural fragment of formula I(iii) or I(iv):



I(iii)



I(iv)

wherein R^5 represents OR^6 or $C(O)OR^7$;

5 R^6 represents H , C_{1-10} alkyl, C_{1-3} alkylaryl or C_{1-3} alkyloxyaryl (the alkyl parts of which latter two groups are optionally interrupted by one or more oxygen atoms, and the aryl parts of which latter two groups are optionally substituted by one or more substituents selected from halo, phenyl, methyl or methoxy, which latter three groups are also optionally substituted by one or more halo substituents);

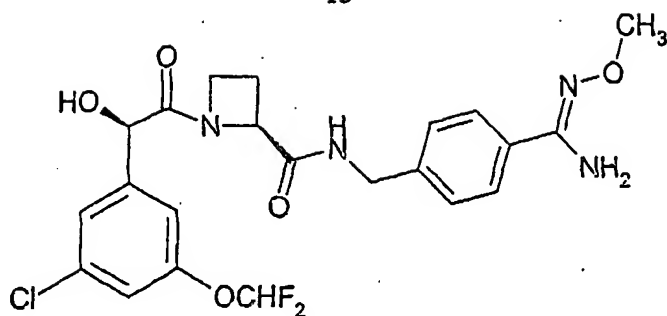
10 R^7 represents C_{1-10} alkyl (which latter group is optionally interrupted by one or more oxygen atoms), or C_{1-3} alkylaryl or C_{1-3} alkyloxyaryl (the alkyl parts of which latter two groups are optionally interrupted by one or more oxygen atoms, and the aryl parts of which latter two groups are optionally substituted by one or more substituents selected from halo, phenyl, methyl or methoxy, which latter three groups are also optionally substituted by one or more halo substituents); and

R^a , R^1 , R^2 , Y , R^4 , X_1 , X_2 , X_3 and X_4 are as hereinbefore defined.

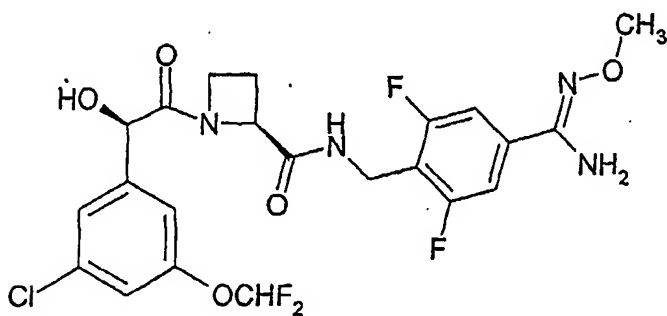
20 Preferred prodrugs of compounds of formula I are methoxyamidine prodrugs thereof. Hence preferred compounds of formula Ia include:

(i) $Ph(3-Cl)(5-OCHF_2)-(R)CH(OH)C(O)-(S)Aze-Pab(OMe)$:

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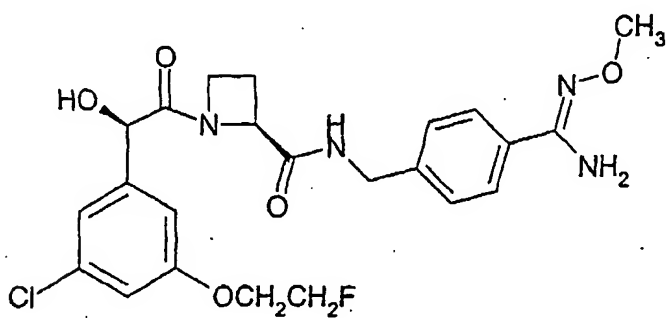


(ii) Ph(3-Cl)(5-OCHF₂)-(R)CH(OH)C(O)-(S)Aze-Pab(2,6-diF)(OMe):



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(iii) Ph(3-Cl)(5-OCH₂CH₂F)-(R)CH(OH)C(O)-(S)Aze-Pab(OMe):



10

Compounds of formulae I and Ia may be made in accordance with techniques described in international patent application WO 02/44145.

- In accordance with the invention, thrombin inhibitors and derivatives thereof may be administered orally, intravenously, subcutaneously, buccally, rectally, dermally, nasally, tracheally, bronchially, topically, by any other parenteral route, or *via* inhalation, in the form of a pharmaceutical preparation comprising the thrombin inhibitor or prodrug in a pharmaceutically acceptable dosage form. Depending on the disorder, and the patient, to be treated, as well as the route of administration, the compositions may be administered at varying doses.
- 10 Preferred modes of delivery are systemic. For melagatran and derivatives thereof, preferred modes of administration are parenteral, more preferably intravenous, and especially subcutaneous. For prodrugs of melagatran and compounds of formula Ia, preferred modes of administration are oral.
- 15 In the therapeutic treatment of mammals, and especially humans, thrombin inhibitors, prodrugs of thrombin inhibitors, and derivatives of either will generally be administered as a pharmaceutical formulation in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, which may be selected with due regard to the intended route of administration and
- 20 standard pharmaceutical practice.

Suitable formulations for use in administering thrombin inhibitors are known in the art, and include those known from US Patent N° 4,346,078; International Patent Applications WO 93/11152, WO 93/18060, WO 93/05069, WO 94/20467, WO 94/29336, WO 95/35309, WO 95/23609, WO 96/03374, WO 96/06832, WO 96/06849, WO 96/17860, WO 96/24609, WO 96/25426, WO 96/32110, WO 97/01338, WO 97/02284, WO 97/15190, WO 97/30708, WO 97/40024, WO 97/46577, WO 98/06740, WO 97/49404, WO 97/11693, WO 97/24135, WO 97/47299, WO 98/01422, WO 98/57932, WO

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Suitable formulations for use with melagatran, derivatives and prodrugs thereof are described in the literature, for example as described in *inter alia* international patent applications WO 94/29336, WO 96/14084, WO 96/16671, WO 97/23499, WO 97/39770, WO 97/45138, WO 98/16252, WO 15 99/27912, WO 99/27913, WO 00/12043 and WO 00/13671, the disclosures in which documents are hereby incorporated by reference. Otherwise, the preparation of suitable formulations may be achieved non-inventively by the skilled person using routine techniques.

20 The amounts of thrombin inhibitor or derivative in the formulation will depend on the severity of the condition, and on the patient, to be treated, as well as the compound(s) which is/are employed, but may be determined non-inventively by the skilled person.

25 Suitable doses of thrombin inhibitors and derivatives thereof in the therapeutic and/or prophylactic treatment of mammalian, especially human, patients may be determined routinely by the medical practitioner or other skilled person, and include the respective doses discussed in the relevant

prior art documents that are mentioned hereinbefore, the relevant disclosures in which are hereby incorporated by reference.

In the case of melagatran, suitable doses of active compound, prodrugs and derivatives thereof, in the therapeutic and/or prophylactic treatment of mammalian, especially human, patients include those which give a mean plasma concentration of up to 5 $\mu\text{mol/L}$, for example in the range 0.001 to 5 $\mu\text{mol/L}$ over the course of treatment of the relevant condition. Suitable doses may thus be in the range 0.1 mg once daily to 25 mg three times daily, and/or up to 100 mg infused parenterally over a 24 hour period, for melagatran, and in the range 0.1 mg once daily to 100 mg three times daily for prodrugs of melagatran (see also the specific doses mentioned hereinafter for the prodrug of melagatran, ximelagatran).

In the case of compounds of formulae I and Ia, suitable daily doses of compounds in the therapeutic treatment of humans are about 0.001-100 mg/kg body weight at peroral administration and 0.001-50 mg/kg body weight at parenteral administration.

In any event, the physician, or the skilled person, will be able to determine the actual dosage which will be most suitable for an individual patient, which is likely to vary with the severity of the condition that is to be treated, as well as the age, weight, sex and response of the particular patient to be treated. The above-mentioned dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Low molecular weight thrombin inhibitors may be employed in the method described herein by way of co-administration along with other cholesterol-

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lowering, or lipid-lowering/modifying, drugs/therapies that are mentioned hereinbefore, such as the statins (HMG-CoA reductase inhibitors) and particularly any one of those statins specifically mentioned hereinbefore, in combination therapy.

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According to a further aspect of the invention, there is provided a combination product comprising:

- (A) a low molecular weight thrombin inhibitor, or a pharmaceutically-acceptable derivative thereof; and
- 10 (B) another cholesterol-lowering, or lipid-lowering/modifying, therapeutic agent,

wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

- 15 Such combination products provide for the administration of low molecular weight thrombin inhibitor/derivative in conjunction with the other therapeutic agent, and may thus be presented either as separate formulations, wherein at least one of those formulations comprises thrombin inhibitor/derivative, and at least one comprises the other therapeutic agent,
- 20 or may be presented (i.e. formulated) as a combined preparation (i.e. presented as a single formulation including thrombin inhibitor/derivative and the other therapeutic agent).

Thus, there is further provided:

25

- (1) a pharmaceutical formulation including a low molecular weight thrombin inhibitor, or a pharmaceutically-acceptable derivative thereof; another cholesterol-lowering, or lipid lowering/modifying, therapeutic agent; and a pharmaceutically-acceptable adjuvant, diluent or carrier; and

- (2) a kit of parts comprising components:
- (a) a pharmaceutical formulation including a low molecular weight thrombin inhibitor, or a pharmaceutically-acceptable derivative thereof, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and
 - (b) a pharmaceutical formulation including another cholesterol-lowering, or lipid lowering/modifying, therapeutic agent in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,
- 10 which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

The method described herein may have the advantage that, in cholesterol-lowering therapy, it may be more convenient for the physician and/or patient
15 than, be more efficacious than, be less toxic than, have a broader range of activity than, be more potent than, produce fewer side effects than, or that it may have other useful pharmacological properties over, similar methods (treatments) known in the prior art for use in such therapy.

20 The invention is illustrated, but in no way limited, by the following examples, in which:

Figure 1 illustrates the difference in mean values (with 95% Confidence Intervals) of total cholesterol levels in serum as between patients receiving
25 ximelagatran (36 mg bid) or warfarin (INR levels between 2 and 3) during the course of a clinical trial over a 21 month period.

Figure 2 illustrates the difference in mean values (with 95% Confidence Intervals) of levels of total triglycerides in serum as between patients

receiving ximelagatran (36 mg bid) or warfarin (INR levels between 2 and 3) during the course of a clinical trial over a 21 month period.

Figure 3 illustrates the difference in mean values (with 95% Confidence Intervals) of LDL (i.e. LDL-cholesterol) levels in serum as between patients receiving ximelagatran (36 mg bid) or warfarin (INR levels between 2 and 3) during the course of a clinical trial over a 21 month period.

Figure 4 illustrates the difference in mean values (with 95% Confidence Intervals) of HDL (i.e. HDL-cholesterol) levels in serum as between patients receiving ximelagatran (36 mg bid) or warfarin (INR levels between 2 and 3) during the course of a clinical trial over a 21 month period.

Example 1

Lipid Measurements in Patients Undergoing Thrombin Inhibition Therapy in a Clinical Trial

A large-scale Phase III clinical trial was set up to establish the efficacy of the study compound $\text{EtO}_2\text{C}-\text{CH}_2-(R)\text{Cgl}-(S)\text{Aze-Pab-OH}$ (ximelagatran; see Example 17 of international patent application WO 97/23499) in the prevention of stroke in patients with non-valvular atrial fibrillation, as compared to the current frontline treatment for this indication, warfarin.

Ximelagatran is a prodrug of the low molecular weight thrombin inhibitor, melagatran (see Example 1 of international patent application WO 94/29226).

The clinical trial protocol was similar to that described in international patent application WO 02/36157, with the following major differences:

20

- (a) the study objective was to show that the efficacy of ximelagatran is non-inferior to that of dose-adjusted warfarin, aiming for an INR 2.0-3.0 (with INR measurements taken at least every 28 ± 3 days), in the prevention of all strokes (fatal and non-fatal) and systemic embolic events in patients with chronic non-valvular atrial fibrillation;
- (b) the dosage of ximelagatran was fixed at 36 mg bid;
- (c) in the exclusion criteria, subjects who had experienced stroke within the previous 30 days or transient ischaemic attack within the previous 3 days were excluded (as opposed to 2 years in the study described in WO 02/36157);
- (d) the duration of treatment was long term (between 12 and 26 months); and
- (e) the total number of patients in the trial was 3407 (as opposed to 220 in the study described in WO 02/36157). The study was a multicentre, multinational, IVRS-randomised, open-label, parallel-group study carried out across approximately 300 centres in approximately 25 countries.

Over the first 21 months of the trial, blood samples were taken from all patients in a standard manner at the following intervals: beforehand, and at 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, and 21, months. These samples were routinely analysed for total cholesterol, LDL (i.e. LDL-cholesterol), HDL (i.e. HDL-cholesterol), and total triglycerides, content using standard techniques for the detection of these lipids in serum.

A comparison was made between patients on ximelagatran ($n = 1704$) and warfarin ($n = 1703$). When the raw data were analysed, an unexpected statistically-significant difference in favour of the ximelagatran group was observed. As of the second month of treatment, marked mean differences

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were observed for cholesterol, triglycerides and LDL serum concentrations (consistently significantly lower in the ximelagtran group over the entire 21 month period), and for the HDL serum concentration (consistently significantly higher in the ximelagtran group over the entire 21 month
5 period), as illustrated in Figures 1 to 4, respectively.

These data clearly demonstrate the potential utility of melagatran and derivatives thereof (e.g. prodrugs, such as ximelagtran), as well as, potentially, low molecular weight thrombin inhibitors and
10 derivatives/prodrugs thereof, in cholesterol-lowering therapy.

Claims

1. The use of a low molecular weight thrombin inhibitor, or a
5 pharmaceutically acceptable derivative thereof, for the manufacture of a
medicament for use in cholesterol-lowering therapy.
2. The use of a low molecular weight thrombin inhibitor, or a
pharmaceutically acceptable derivative thereof, for the manufacture of a
10 medicament for the treatment of hypercholesterolaemia,
hyperlipoproteinaemia and/or hypertriglyceridaemia.
3. The use as claimed in Claim 1 or Claim 2, wherein the therapy/treatment
results in a decrease in serum levels of cholesterol, low-density lipoproteins,
15 very low-density lipoproteins, triglycerides and/or apolipoprotein B; and/or
an increase in serum levels of high-density lipoproteins and/or
apolipoprotein A-I.
4. The use as claimed in any one of the preceding claims, wherein the
20 thrombin inhibitor is melagatran.
5. The use as claimed in Claim 4, wherein the derivative of melagatran is a
prodrug of melagatran.
- 25 6. The use as claimed in Claim 5, wherein the prodrug is of the formula
$$R^1O_2C-CH_2-(R)Cgl-(S)Aze-Pab-OH,$$
wherein R^1 represents linear or branched C_{1-6} alkyl and the OH group
replaces one of the amidino hydrogens in Pab.

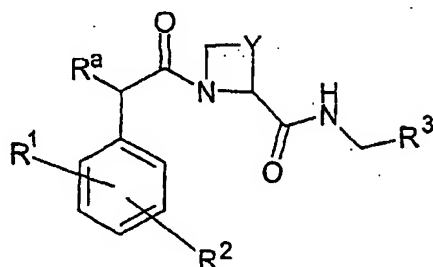
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7. The use as claimed in Claim 6, wherein R^1 represents methyl, ethyl or propyl.

8. The use as claimed in Claim 7, wherein R^1 represents ethyl.

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9. The use as claimed in any one of Claims 1 to 3, wherein the thrombin inhibitor is of formula I,



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wherein

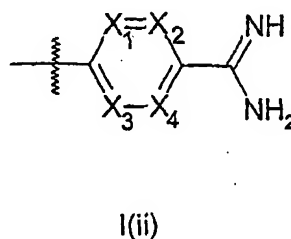
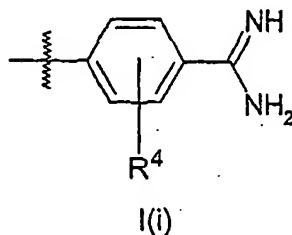
R^a represents -OH or -CH₂OH;

R^1 represents at least one optional halo substituent;

R^2 represents one or two C₁₋₃ alkoxy substituents, the alkyl parts of which
15 substituents are themselves substituted with one or more fluoro substituents;

Y represents -CH₂- or -(CH₂)₂-; and

R^3 represents a structural fragment of formula I(i) or I(ii):



20 wherein

R^4 represents H or one or more fluoro substituents; and

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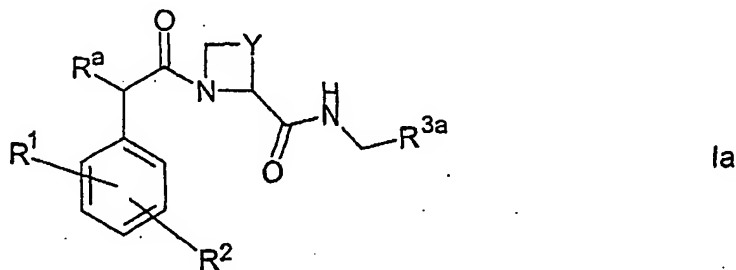
one or two of X_1 , X_2 , X_3 and X_4 represent -N- and the others represent -CH-.

10. The use as claimed in Claim 9, wherein the thrombin inhibitor is:

- 5 Ph(3-Cl)(5-OCHF₂)-(R)CH(OH)C(O)-(S)Aze-Pab;
 Ph(3-Cl)(5-OCHF₂)-(R)CH(OH)C(O)-(S)Aze-Pab(2,6-diF); or
 Ph(3-Cl)(5-OCH₂CH₂F)-(R)CH(OH)C(O)-(S)Aze-Pab.

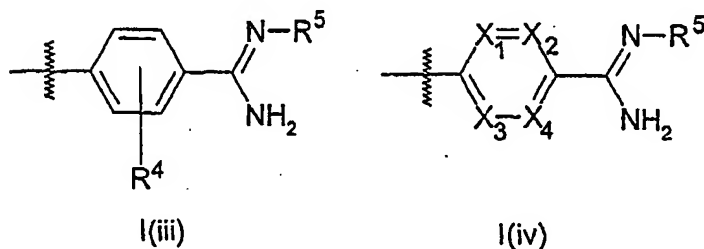
11. The use as claimed in Claim 9 or Claim 10, wherein the derivative of
 10 the thrombin inhibitor is a prodrug of that inhibitor.

12. The use as claimed in Claim 11, wherein the prodrug is of formula Ia,



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wherein R^{3a} represents a structural fragment of formula I(iii) or I(iv):



20 wherein R^5 represents OR^6 or $C(O)OR^7$;

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R^6 represents H, C_{1-10} alkyl, C_{1-3} alkylaryl or C_{1-3} alkyloxyaryl (the alkyl parts of which latter two groups are optionally interrupted by one or more oxygen atoms, and the aryl parts of which latter two groups are optionally substituted by one or more substituents selected from halo, phenyl, methyl or methoxy, which latter three groups are also optionally substituted by one or more halo substituents);

R^7 represents C_{1-10} alkyl (which latter group is optionally interrupted by one or more oxygen atoms), or C_{1-3} alkylaryl or C_{1-3} alkyloxyaryl (the alkyl parts of which latter two groups are optionally interrupted by one or more oxygen atoms, and the aryl parts of which latter two groups are optionally substituted by one or more substituents selected from halo, phenyl, methyl or methoxy, which latter three groups are also optionally substituted by one or more halo substituents); and

R^a , R^1 , R^2 , Y, R^4 , X_1 , X_2 , X_3 and X_4 are as defined in Claim 9.

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13. The use as claimed in Claim 12, wherein the prodrug is:

$\text{Ph}(3\text{-Cl})(5\text{-OCHF}_2)\text{-(R)CH(OH)C(O)-(S)Aze-Pab(OMe)}$;

$\text{Ph}(3\text{-Cl})(5\text{-OCHF}_2)\text{-(R)CH(OH)C(O)-(S)Aze-Pab}(2,6\text{-diF})(\text{OMe})$; or

$\text{Ph}(3\text{-Cl})(5\text{-OCH}_2\text{CH}_2\text{F})\text{-(R)CH(OH)C(O)-(S)Aze-Pab(OMe)}$.

20

14. A cholesterol-lowering therapy method, which method comprises the administration of a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative thereof, to a patient in need of such therapy.

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15. A method of treatment of hypercholesterolaemia, hyperlipoproteinaemia and/or hypertriglyceridaemia, which method comprises the administration of a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative thereof, to a patient in need of such treatment.

16. The method as claimed in Claim 14 or Claim 15 wherein the therapy/treatment results in a decrease in serum levels of cholesterol, low-density lipoproteins, very low-density lipoproteins, triglycerides and/or apolipoprotein B; and/or an increase in serum levels of high-density lipoproteins and/or apolipoprotein A-I.

17. The method as claimed in any one of Claims 14 to 16, wherein the thrombin inhibitor is melagatran.

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18. The method as claimed in Claim 17, wherein the derivative of melagatran is a prodrug of melagatran.

19. The method as claimed in Claim 18, wherein the prodrug is of the formula



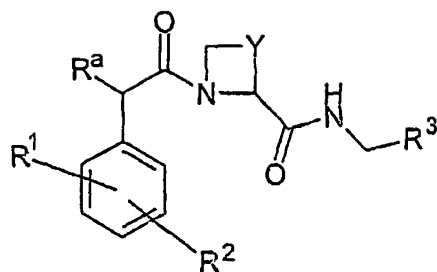
wherein R^1 represents linear or branched C_{1-6} alkyl and the OH group replaces one of the amidino hydrogens in Pab.

20. The method as claimed in Claim 19, wherein R^1 represents methyl, ethyl or propyl.

21. The method as claimed in Claim 20, wherein R^1 represents ethyl.

22. The method as claimed in any one of Claims 14 to 16, wherein the thrombin inhibitor is of formula I,

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wherein

R^a represents -OH or -CH₂OH;

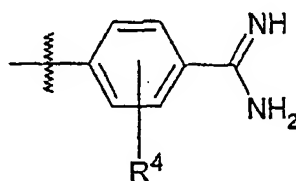
5 R¹ represents at least one optional halo substituent;

R² represents one or two C₁₋₃ alkoxy substituents, the alkyl parts of which substituents are themselves substituted with one or more fluoro substituents;

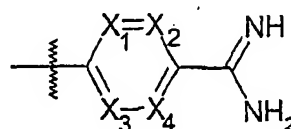
Y represents -CH₂- or -(CH₂)₂-; and

R³ represents a structural fragment of formula I(i) or I(ii):

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I(i)



I(ii)

wherein

R⁴ represents H or one or more fluoro substituents; and

one or two of X₁, X₂, X₃ and X₄ represent -N- and the others represent

15 -CH-.

23. The method as claimed in Claim 22, wherein the thrombin inhibitor is:

Ph(3-Cl)(5-OCHF₂)-(R)CH(OH)C(O)-(S)Aze-Pab;

Ph(3-Cl)(5-OCHF₂)-(R)CH(OH)C(O)-(S)Aze-Pab(2,6-diF); or

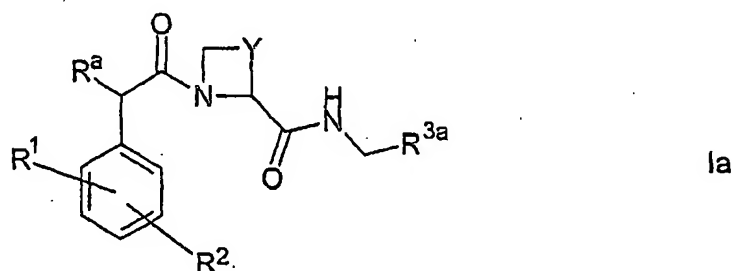
20 Ph(3-Cl)(5-OCH₂CH₂F)-(R)CH(OH)C(O)-(S)Aze-Pab.

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24. The method as claimed in Claim 22 or Claim 23, wherein the derivative of the thrombin inhibitor is a prodrug of that inhibitor.

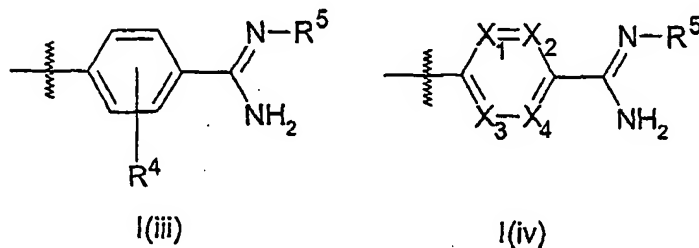
25. The method as claimed in Claim 24, wherein the prodrug is of formula

5 Ia,



wherein R^{3a} represents a structural fragment of formula I(iii) or I(iv):

10



wherein R^5 represents OR^6 or $C(O)OR^7$;

15 R^6 represents H, C_{1-10} alkyl, C_{1-3} alkylaryl or C_{1-3} alkyloxyaryl (the alkyl parts of which latter two groups are optionally interrupted by one or more oxygen atoms, and the aryl parts of which latter two groups are optionally substituted by one or more substituents selected from halo, phenyl, methyl or methoxy, which latter three groups are also optionally substituted by one or more halo substituents);

20 R^7 represents C_{1-10} alkyl (which latter group is optionally interrupted by one or more oxygen atoms), or C_{1-3} alkylaryl or C_{1-3} alkyloxyaryl (the alkyl parts

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of which latter two groups are optionally interrupted by one or more oxygen atoms, and the aryl parts of which latter two groups are optionally substituted by one or more substituents selected from halo, phenyl, methyl or methoxy, which latter three groups are also optionally substituted by one or more halo substituents); and
5 R^a , R^1 , R^2 , Y , R^4 , X_1 , X_2 , X_3 and X_4 are as defined in Claim 22.

26. The method as claimed in Claim 25, wherein the prodrug is:

Ph(3-Cl)(5-OCHF₂)-(R)CH(OH)C(O)-(S)Aze-Pab(OMe);
10 Ph(3-Cl)(5-OCHF₂)-(R)CH(OH)C(O)-(S)Aze-Pab(2,6-diF)(OMe); or
Ph(3-Cl)(5-OCH₂CH₂F)-(R)CH(OH)C(O)-(S)Aze-Pab(OMe).

27. A combination product comprising:

(A) a low molecular weight thrombin inhibitor, or a pharmaceutically-
15 acceptable derivative thereof; and
(B) another cholesterol-lowering, or lipid-lowering/modifying,
therapeutic agent,

wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

20

28. A combination product as claimed in Claim 27, which comprises a pharmaceutical formulation including the thrombin inhibitor or derivative, the other therapeutic agent and a pharmaceutically-acceptable adjuvant, diluent or carrier.

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29. A combination product as claimed in Claim 27, which comprises a kit of parts comprising components:

30

(a) a pharmaceutical formulation including the thrombin inhibitor, or derivative, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

5 (b) a pharmaceutical formulation including the other therapeutic agent in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

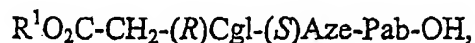
which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

10 30. A combination product as claimed in any one of Claims 27 to 29, wherein the thrombin inhibitor is melagatran.

31. A combination product as claimed in Claim 30, wherein the derivative of melagatran is a prodrug of melagatran.

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32. A combination product as claimed in Claim 31, wherein the prodrug is of the formula

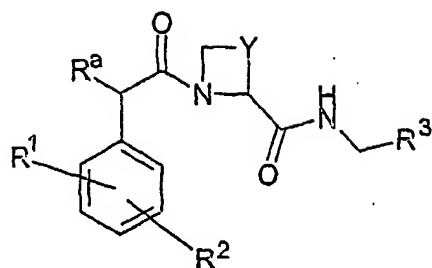


wherein R^1 represents linear or branched C_{1-6} alkyl and the OH group
20 replaces one of the amidino hydrogens in Pab.

33. A combination product as claimed in Claim 32, wherein R^1 represents methyl, ethyl or propyl.

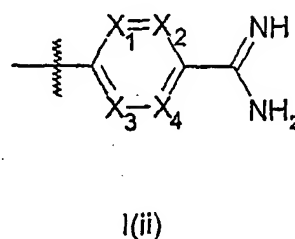
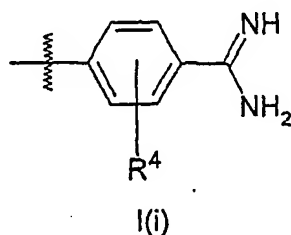
25 34. A combination product as claimed in Claim 33, wherein R^1 represents ethyl.

35. A combination product as claimed in any one of Claims 27 to 29, wherein the thrombin inhibitor is of formula I,



wherein

- 5 R^a represents -OH or -CH₂OH;
 R^1 represents at least one optional halo substituent;
 R^2 represents one or two C₁₋₃ alkoxy substituents, the alkyl parts of which substituents are themselves substituted with one or more fluoro substituents;
Y represents -CH₂- or -(CH₂)₂; and
10 R^3 represents a structural fragment of formula I(i) or I(ii):



wherein

- R^4 represents H or one or more fluoro substituents; and
15 one or two of X₁, X₂, X₃ and X₄ represent -N- and the others represent -CH-.

36. A combination product as claimed in Claim 35, wherein the thrombin inhibitor is:

- 20 Ph(3-Cl)(5-OCHF₂)-(R)CH(OH)C(O)-(S)Aze-Pab;
Ph(3-Cl)(5-OCHF₂)-(R)CH(OH)C(O)-(S)Aze-Pab(2,6-diF); or

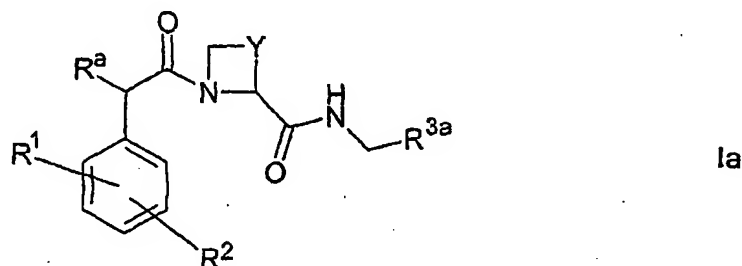
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Ph(3-Cl)(5-OCH₂CH₂F)-(R)CH(OH)C(O)-(S)Aze-Pab.

37. A combination product as claimed in Claim 35 or Claim 36, wherein the derivative of the thrombin inhibitor is a prodrug of that inhibitor.

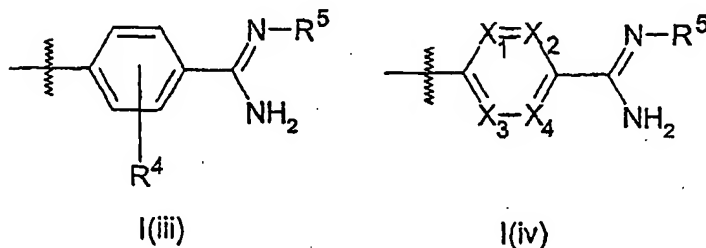
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38. A combination product as claimed in Claim 37, wherein the prodrug is of formula Ia,



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wherein R^{3a} represents a structural fragment of formula I(iii) or I(iv):



15' wherein R⁵ represents OR⁶ or C(O)OR⁷;

R⁶ represents H, C₁₋₁₀ alkyl, C₁₋₃ alkylaryl or C₁₋₃ alkyloxyaryl (the alkyl parts of which latter two groups are optionally interrupted by one or more oxygen atoms, and the aryl parts of which latter two groups are optionally substituted by one or more substituents selected from halo, phenyl, methyl or methoxy, which latter three groups are also optionally substituted by one or more halo substituents);

20

R⁷ represents C₁₋₁₀ alkyl (which latter group is optionally interrupted by one or more oxygen atoms), or C₁₋₃ alkylaryl or C₁₋₃ alkyloxyaryl (the alkyl parts of which latter two groups are optionally interrupted by one or more oxygen atoms, and the aryl parts of which latter two groups are optionally substituted by one or more substituents selected from halo, phenyl, methyl or methoxy, which latter three groups are also optionally substituted by one or more halo substituents); and

R^a, R¹, R², Y, R⁴, X₁, X₂, X₃ and X₄ are as defined in Claim 35.

10 39. A combination product as claimed in Claim 38, wherein the prodrug is:

Ph(3-Cl)(5-OCHF₂)-(R)CH(OH)C(O)-(S)Aze-Pab(OMe);

Ph(3-Cl)(5-OCHF₂)-(R)CH(OH)C(O)-(S)Aze-Pab(2,6-diF)(OMe); or

Ph(3-Cl)(5-OCH₂CH₂F)-(R)CH(OH)C(O)-(S)Aze-Pab(OMe).

15 40. A combination product as claimed in any one of Claims 27 to 39, wherein the other therapeutic agent is a statin.

41. A combination product as claimed in Claim 40 wherein the statin is lovastatin, pravastatin, fluvastatin, simvastatin, atorvastatin, pitavastatin or
20 rosuvastatin.

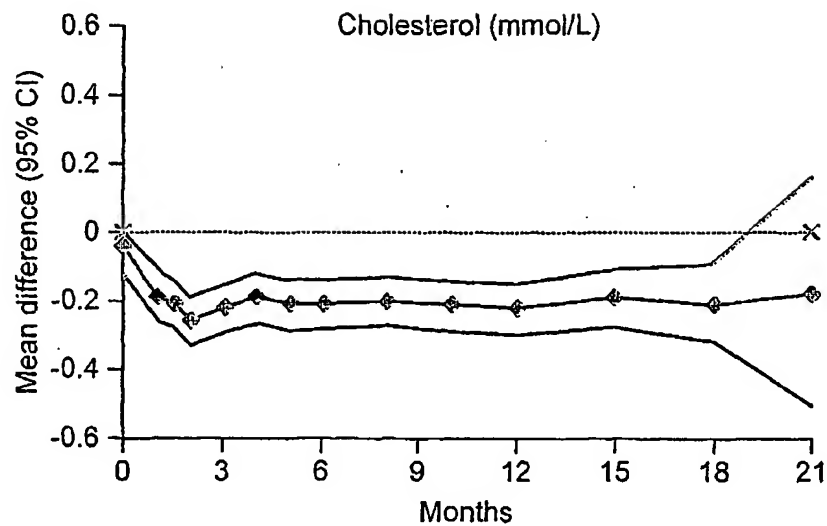
42. A pharmaceutical formulation for use in cholesterol-lowering therapy, which formulation comprises an effective amount of a low molecular weight thrombin inhibitor, or a pharmaceutically-acceptable derivative thereof.

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43. Use of a low molecular weight thrombin inhibitor, or a pharmaceutically-acceptable derivative thereof, in cholesterol-lowering therapy, by administering that inhibitor, or pharmaceutically-acceptable derivative, to a patient.

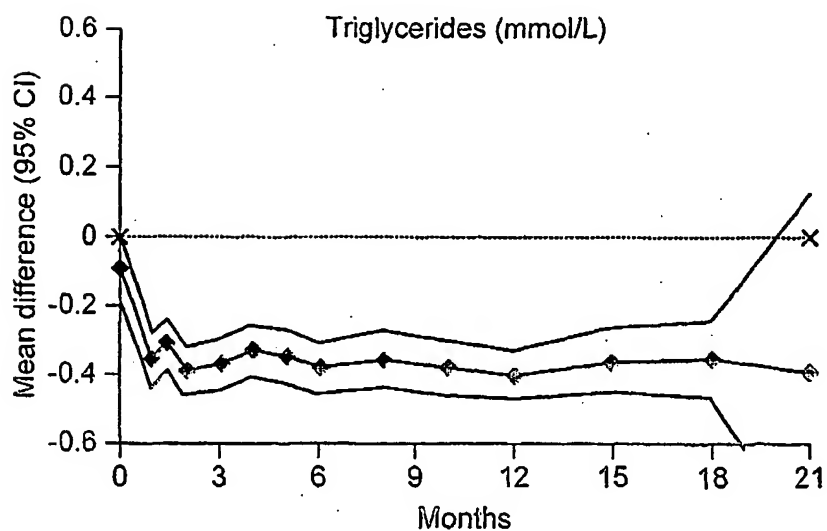
44. The use of a low molecular weight thrombin inhibitor, or a pharmaceutically-acceptable derivative thereof, in cholesterol-lowering therapy.

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Mean at baseline: ximelagatran 5.27, warfarin 5.32

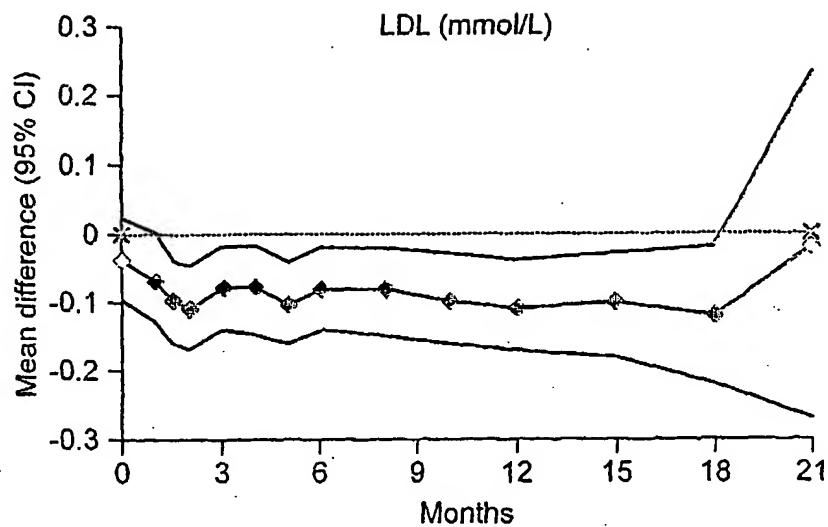
FIG. 1



Mean at baseline: ximelagatran 1.86, warfarin 1.95

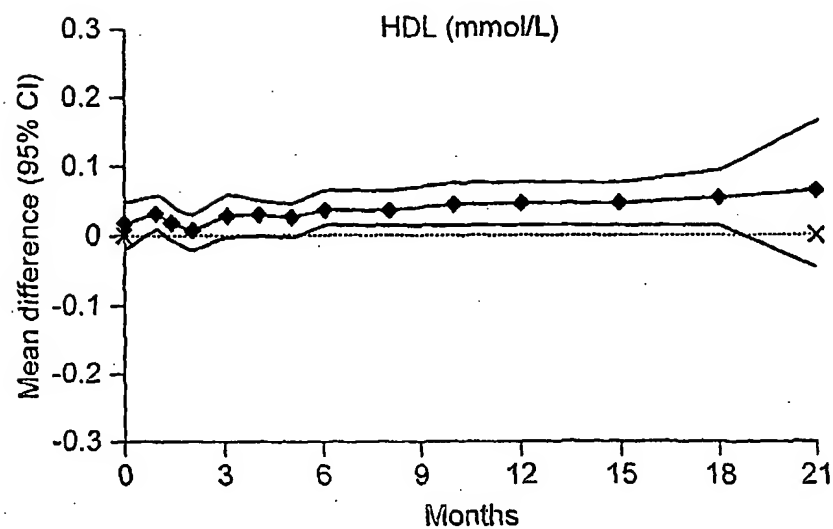
FIG. 2

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Mean at baseline: ximelagatran 3.14, warfarin 3.18

FIG. 3



Mean at baseline: ximelagatran 1.31, warfarin 1.28

FIG. 4

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 2004/000417

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 38/05, A61P 7/02, A61K 3/06, A61K 3/10
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM. ABS DATA, WPI DATA, EMBASE, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0432537 A2 (IKETON FARMACEUTICI S.R.L.), 19 June 1991 (19.06.1991), see page 2, lines 29-32 and page 4, lines 25-26 --	1-26,42-44
X	WO 9811896 A1 (MERCK & CO., INC.), 26 March 1998 (26.03.1998), see the claims and page 22, lines 27-29 -- -----	27-41

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

30 June 2004

Date of mailing of the international search report

01-07-2004

Name and mailing address of the ISA/
Swedish Patent Office
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Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/000417

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **15-26, 43**
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet*
2. ☒ Claims Nos.: **1-2, 27**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see next sheet**
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/000417

*

Claims 15-26, 43 relate to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practised on the human or animal body (PCT Rule 39.1(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds or compositions.

**

Present claims 1-2 and 27 relate to compounds defined by reference to a desirable characteristic or property, namely low molecular weight thrombin inhibitor, cholesterol-lowering or lipid-lowering therapeutic agents. The claims cover the use of all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT or disclosure within the meaning of Article 5 PCT for only a very limited number of such. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to compounds defined in claims 4-13. A search for the general wording "low molecular weight thrombin inhibitor" have also been made.

INTERNATIONAL SEARCH REPORT

Information on patent family members

30/04/2004

International application No.

PCT/SE 2004/000417

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